

Biological and therapeutic properties of bee venom

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THE PAINFUL HEALING STINGS: BEE VENOM IN HUMAN HISTORY

Whether the humans began keeping bees because of the healing effects of their stings or to get honey, or for both reasons, we do not know. Already in the early ancient civilizations know about the healing found virtues in the painful bee stings. Bee stings are probably one of the first natural cure for arthritis. In the ancient civilization of China, India, Egypt, Babylon and Greece bee venom was used for apitherapy¹²⁷.

In Huandi Neijing, an ancient Chinese medical book, around 500 BC, bee sting therapy was mentioned¹⁷.

Around 300 BC Aristoteles, referred to the stinging apparatus of bees and the powerful properties of bee venom (BV) in his book *Historia animalia*¹²⁷.

The ancient Greek doctor Hippocrates used bee venom for therapeutic purposes. He described it as *Arcanum*, a mysterious substance whose curative properties he did not quite understand.

In 14 BC Pliny the elder described BV use in his Natural history. Galen (130–200 AD) prescribed the use of honey and bee venom as a cure for baldness⁴⁸

It is documented that Charlemagne (742-814) received bee stings for therapy against gout, while Monfat (1566-1634) prescribed bee stings to improve the flow of urine and against kidney stones after²³.

In 1609 C. Butler mentioned the sting organ of bees in his book *Feminine Monarchie*. In 1672 Jan Swammerdam provided a thorough description of bees' venom apparatus. In 1834 L. Dufour described the venom gland, which was later found out to contain an alkaline solution, thence known as the alkaline or Dufour's gland after. In 1737 Samuel Dave in his *Pharmacologia* recommended *Apis* for baldness and as a good diuretic. In 1858 the French medical doctor de Marti began to use bee stings for treatment of several diseases. In 1858 C.W. Wolf a prominent homeopathic physician of Berlin edited his book *Apis Mellifica or the poison of the honey bee considered as a therapeutic agent*. In 1868 the Russians Lokumski and Lubarski published a work named "Bee venom, a remedy"^{10, 127}.

The modern use of BV in apitherapy was initiated through the efforts of Austrian physician Philip Terc in his published results "Report about a Peculiar Connection between the Bee Stings and Rheumatism" in 1888¹²⁴.

After the first world war Bodog Beck brought BV apitherapy to the US and published a book on BV therapy in 1935, mainly against rheumatoid arthritis. In Europe the first commercial bee venom preparation was released in 1928¹⁰. Charles Mraz, a student of Beck, popularised BV therapy in the USA⁹⁴.

BIOLOGICAL ACTION OF BEE VENOM AND ITS COMPONENTS

Of all bee products bee venom (BV) produces by far the greatest number of biological effects. BV is the bee product, with the highest recognition in modern medicine, many of its components being also used in experimental pharmacology¹³.

Beneficial biological effects of whole bee venom in animal and cell experiments

Overall effect or target	Specific effects	Reference
<i>Anti-inflammatory and anti-arthritis action</i>	glucocorticoid-and aspirin like effects, blocking of proinflammatory substances, modification of the cell membrane	6, 70, 87, 119, 122, 127
<i>Anti-cancer effects</i>	Antitumor effects on ovary, hepatoma, prostate, bladder, melanoma and renal cancers cells by different mechanisms of action depending on the tumor type	6, 70, 87, 103, 119, 122, 127
<i>Affects the central and peripheral nervous system</i> (CNS, PNS)	<ul style="list-style-type: none"> Stimulates many peripheral chemoreceptors affecting flow to the CNS Has cholinolytic action (against acetylcholine) Blocks transmission of the vegetative synapse and the polysynaptic neuronal paths Pain-soothing aspirin-like action Management of chronic and inflammatory pain Influence of brain EEG and behaviour patterns Increases brain blood circulation Prevents neuronal cell death caused by prion peptides Anti-MS in a rat model Against oxaliplatin-induced neuropathy 	6, 55, 58-60, 70, 81, 87, 119, 122, 127, 136
<i>Anti-addictive effects</i>	BV acupuncture may modulate methamphetamine-induced hyperactivity	68
<i>Heart and blood system</i>	<ul style="list-style-type: none"> Increases coronary and peripheral blood circulation, improves the microcirculation of blood in the tissues, Slows down heart at lower doses and stimulates it at higher ones, lowers blood pressure, antiarrhythmic Against blood coagulation fibrinolytic, stimulates the building of erythrocytes 	6, 70, 87, 119, 122, 127
<i>Anticancer</i>	In renal, lung, liver, prostate, bladder melanoma, osteosarcoma, mammary cancer cells and leukemia cells	102, 122
<i>Against Benigh Prostate Hyperplasia</i>	Inhibits testosterone induced hyperplasia in rats	22
<i>Action on the immune system</i>	Immunosuppressive (high doses) and immunoactivating (lower doses)	6, 37, 70, 87, 119, 122, 127
<i>Protection from radiation</i>	Improves regeneration of leucocytes and erythrocytes	6, 70, 87, 119, 122, 127
<i>Antibiotic, fungicide and antiviral action</i>	Bactericide action against different pathogens, also <i>Lyme spirochete</i> ; <i>Candida albicans</i> ; inactivation of Herpes, Leukaemia, HIV, Influenza A (PR8), Vesicular Stomatitis (VSV), Respiratory Syncytial (RSV), Enterovirus-71 (EV-71) and Coxsackie (H3)- viruses	2, 5, 12, 32, 84, 85, 87, 126, 127, 130
<i>Antihyperthermic</i>	Activates specific body systems to overcome hyperthermia	70, 87, 119
<i>Gall bladder-intestine system</i>	Increases fall flow and cholesterine and bilirubin concentrations	87
<i>Endocrinological system</i>	Increases secretion of thyroid, hypophysis and of the hypothalamus hormones	6, 87
<i>Metabolic effects</i>	Increases protein and nucleotide metabolism	87
<i>Against Obesity</i>	In diet induced obesity in rats	18
<i>Liver protecting</i>	Potent suppressive effect on anti-apoptotic responses of TNF-alpha/Act D-treated hepatocytes	105
<i>Growth increasing</i>	Increase of growth of chicken broilers	40
<i>Reno protecting</i>	As tested in artificially induced nephrotoxicity in mice	64
<i>Neuro-protective</i>	As tested in Parkinson model mice	21
<i>Against the Lyme disease</i>	Melittin inhibitis <i>Borrelia burgdorferi</i> .	85
<i>Wound healing</i>	Promotes skin cell regeneration	43
<i>Immunoprophylactic</i>	BV Spray reduces antibiotic use in broilers	56
<i>Against polycystic ovarian syndrome</i>	Decreases the C-reactive protein	61
<i>Anti-diabetic</i>	Lowers blood glucose and increases insulin secretion	93
<i>Against skin itching</i>	Inhibits the mast cell degranulation and cytokine expression	67

Main biological and therapeutic effects of bee venom and its components, after ^{6, 25, 51, 55, 73, 74, 87, 92, 119, 122, 127}**Fonts in red: potentially toxic effects**

Component, % of total	Effect	Tox. mg/kg
Melittin 50-55 % <i>Biologically active peptide</i>	Main biologically active component Membrane-active, diminishes surface tension of membranes and stabilises them, anti-inflammatory in very small doses; stimulates smooth muscles; activates the hypophysis and adrenal glands; increases capillary permeability increasing blood circulation and lowering the blood pressure, lowers blood coagulation, immunostimulatory and immunosuppressive; radiation protective, influences the central nervous system; anticancer, antibacterial, antifungal, antiviral, anticancer, antibacterial, antifungal, antiviral, anti-atherosclerosis, endosomolytic (helps packaging components for gene therapy)	4
Phospholipase A 2 10-12 % <i>Enzyme hydrolysing phospholipids</i>	Immunomodulatory; Neurodegenerative diseases as Parkinson; MS, Alzheimers; anti-inflammatory: against different inflammatory diseases, including lupus nephritis, cisplatin-induced nephrotoxicity, hepatotoxicity and allergic asthma; against acute lung inflammation induced by radiotherapy; antinociceptive, anticancer, anti-bacterial, anti-parasitic and immunotherapeutic effect Destroys phospholipids and dissolves the cell membrane of blood bodies; lowers the blood coagulation and blood pressure, prevents neuronal cell death caused by prion peptides; Induces inflammation, the strongest allergen and thus the most harmful BV component	7.5
Phospholipase B 1 % <i>cleavage of the toxic lysolecetin</i>	Detoxicating activity	
Hyaluronidase 1-2 % <i>Catalyses hydrolysis of hyaloronic acid,</i>	Catalyses the hydrolysis of proteins, thus enabling the penetrating of BV into the tissue; dilates blood vessels and increases their permeability, causing an increase of blood circulation; allergenic	0
Apamin 2-3 % <i>Biologically active peptide</i>	Anti-inflammatory stimulating the release of cortisone, antiserotonine action, preserves red blood cells. increases the defence capability; anticomplementary; activates the hypophysis and adrenal glands; immunosuppressor, specific effects in the brain that might be linked to Alzheimer und MS diseases, anti-Parkinson, Higher doses are neurotoxic	4
MCD, 2-3 % mast cell degranulating-peptide 401	Lyses mast cells, releasing histamine, serotonin and heparine Melittin-like effect increasing capillary permeability increasing anti-inflammatory, simulates the central nervous system	40
Adolapin 1 % <i>Biologically active peptide</i>	Inhibits the specific brain enzymes cyclooxygenase and lipooxygenase Decreases inflammations by, anti-rheumatic, decreases pain, antipyretic Inhibits the aggregation of erythrocytes Has relatively low toxicity	
Protease-Inhibitors 3-5 % <i>Biologically active peptides</i> Secapin, tertiapin, cardiopep, minimin, procamine 3-5 % Histamine 0.7-1.5 % <i>Neurotransmitter</i>	Inhibits the activity of different proteases like trypsin, chymotrypsin, plasmin, thrombin, thus decreasing inflammation, anti-rheumatic Peptides, with an uncertain role in the physiological action of BV Antiradiation effects cardiopep has antiarrhythmic effects Dilates blood vessels, increasing the permeability of blood capillaries and increases blood circulation; Stimulates smooth muscles; Allergenic	192-445
Dopamine, Noradrenaline 0.2-1.5 % <i>Neurotransmitters</i>	The low concentrations in BV do not cause physiological effects in mammals, but active when injected in invertebrates	
Alarm pheromones 4-8 %	Complex ethers, causing alarm of the bee colony and its defensive behaviour	

* - only effects, not caused by the BV components, The toxicity "Tox" is measured in rat experiments

In order to achieve definite biological effects, individual bee venom components can be used and are commercially available. The effects of the different components are numerous and partly also opposing.

Melittin is the main BV component with many positive biological effects and a relatively low toxicity, but is also responsible for the pain induced by BV stings¹⁶. The **MCD peptide** and **phospholipase A2 (PA2)** are the two most toxic components. However, it has been recently found out that PA2 has a number of therapeutic properties⁷³. The toxic and therapeutic properties of PA2 are reviewed in 2016⁷⁴

Antioxidant and anti-inflammatory properties of Portuguese BV were not related to the amounts of melittin, apamin and phospholipase A2¹²¹

A US patent on the basis of bee venom-phospholipase A2 which activates a regulatory T cell and suppresses the differentiation of Th1/Th7 has been created. The present polypeptide can be used as a pharmaceutical composition for treating or preventing a disease related to abnormal suppression of regulatory T cell activity, i.e. autoimmune diseases, allergic diseases, or neurodegenerative diseases⁸

It was found that secapim from *A.cerana* has anti-fibrinolytic, anti-microbial and an anti-elastolytic effect⁷⁸

MEDICAL APPLICATIONS

Therapy with bee venom

Disease type	Application, details	Reference
<i>Arthritis</i>	Both osteoarthritis and rheumatic arthritis Rheumatic arthritis being more susceptible to BVT	70, 87, 119, 122, 127
<i>Against frozen shoulder</i>	BV acupuncture	69, 129
<i>Diseases of the central and peripheral nervous system_(CNS, PNS)</i>	<ul style="list-style-type: none"> • Multiple sclerosis, Dementia, Parkinson • Post stroke paralysis • Polyneuritis • Ganglion nerve inflammation • Cerebellar ataxy (muscular disfunction) • Syringomyelia (pain of extremities, headache) • Inflammation of facial nerve • Myopathy (neuromuscular disease) • Trigeminal neuralgia • Posttraumatic inflammation of plexus nerve • Inflammation of arachnoid CNS membrane • Against lower back pain • Epilepsy, Iritis, Iridocytis, Migraine 	1, 70, 71, 87, 114, 117, 118
<i>Heart and blood system</i>	<ul style="list-style-type: none"> • Hypertension • Arteriosclerosis • Endarteritis (chronic inflammation of the inner layer of arteries) • Angina pectoris • Arrhythmia 	70, 71, 87, 114
<i>Skin diseases and treatments</i>	<ul style="list-style-type: none"> • Eczema, dermatitis, psoriasis • Furunculosis (recurring boil) • Healing of cicatrices • Baldness • Acne 	47, 66, 70, 71, 87, 114
<i>Other disease</i>	<ul style="list-style-type: none"> • The lyme disease • Opthamology • Gastroentorology: colitis, ulcers, • Pulmonology: asthma, bronchitis, • Otorinolaringology: pharyngitis, tonsillitis, ear nerve neuritis • Endocrinology • Urology, gynecology • Cancer 	70, 71, 84, 85, 87, 102, 106, 114

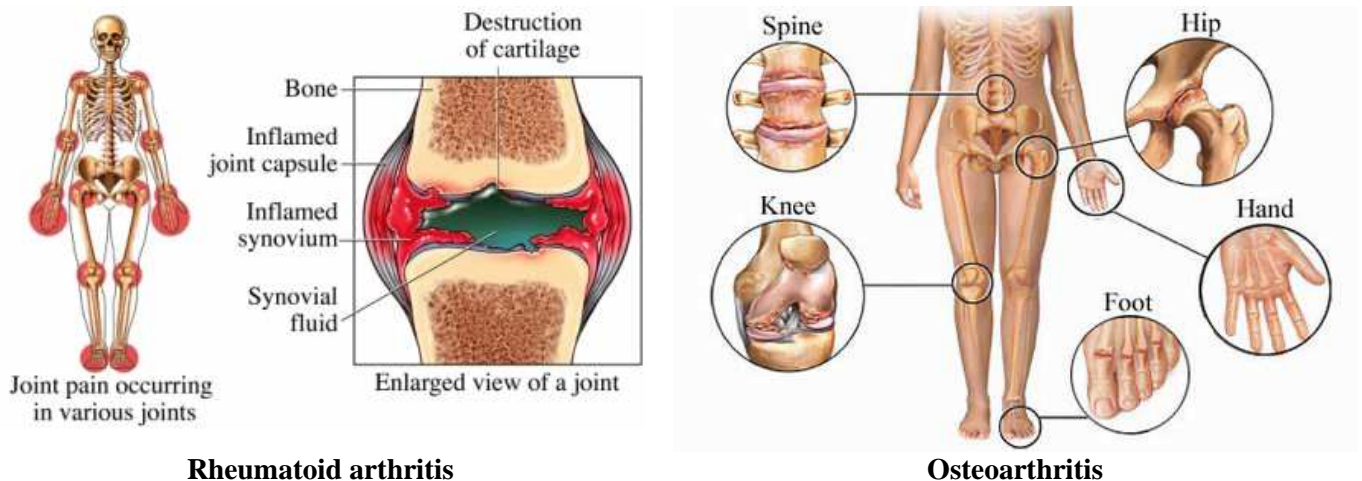
Assuming that arthritis is very old human disease and that Homo sapiens has probably found relief after bee stings, bee stinging is probably the first apitherapy received by humans.

The father of modern apitherapy the Austrian doctor Philip Terc had rheumatism and cured himself by bee stings. Terc hypothesised that the stronger the rheumatism form, the stronger the BV doses should be. He distinguishes three phases of healing: In the first phase the patient develops a pathological immunity with very weak reaction to bee stinging. In the second he is as sensitive to BV as normal people, with the development of a local painful reaction. In this phase healing begins. In the third phase healing is completed. Terc treats his patients with 1 to 50 bees per session. He reports on the treatment of 660 patients. 544 recovered fully, 99 improved and in the remaining 17 the treatment was not successful.

Bodock Beck described modern BV therapy (mostly against arthritis) in his pioneering book carrying the same name, published in 1935¹⁰, available for sale in Amazon as a 1997 pocket book. An extensive Russian monograph by Krylov from 1995⁷⁰ and a 2012 review by Ali³ summarise the medical applications of BV.

Arthritis

There two types of arthritis: **Rheumatoid Arthritis or Polyarthritis (RA)** and **Osteoarthritis (OA)**.



Rheumatoid arthritis or Polyarthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joints producing an inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints. About 1% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men.

The mechanism of action of BV in treating arthritis is clarified:

- BV blocks the building of the pro inflammatory substances cytokine, PGE-2, NO, Tumor Necrosis Factor TNF-2 and Enzyme COX-2
- BV inhibits the proliferation of rheumatoid synovial cells

Osteoarthritis (OA) is the disease process by which joints wear out. As the joint surface wears away it sheds wear particles which stimulate the joint lining to produce fluid, causing the knee to swell. When the articular cartilage wears through, the underlying bone becomes exposed. The exposed bone rubs against exposed bone when walking and this causes pain - often described as a toothache type pain. It is a common disease in adults with a prevalence of about 0.5 %.

There is a very large information data base on the use of BV in OE and RA. Different BV treatments have been used: bee stings (BS), api puncture (AP), injections, electrophoresis and phonophoresis (application with ultrasound waves), the success rates are generally good, lying generally between 60 and 90 %^{70, 87, 119, 122, 127}. During the last 10 year AP has been developed as a new technique for treating arthritis, and is used now most of all in South Korea.

BV does not seem to influence rheumatoid deformation, as shown by patients X-rays, but it acts by controlling pain and inflammation⁷¹.

A review of Lee et al. examined the use of AP in musculoskeletal pain. BV was used in the treatment of different pain conditions: Neck pain, low back pain, herniated lumbar pain, disc pain, shoulder pain after stroke, acute ankle sprain, wrist sprain, rheumatoid arthritis and knee osteoarthritis. BS and AP therapy was useful in all these conditions. AP relieves pain more effectively than acupuncture. However there are no studies comparing stinging in acupuncture points with BV stinging in other body points⁷⁶

Son reviewed clinical trials of the use of BV for the treatment of arthritis by BS and AP, mostly carried out in South Korea. Both RA and OA can be successfully treated.

The success rates in different clinical trials of BV applied as stings, BV injections or apipuncture against RA ranges between 60 and 80 %^{33, 71, 76, 122}. BV api-puncture is as effective as cortisol treatment or RA as tested in arthritic rats⁵⁷

Ludyansky has reviewed the vast experience in Russian hospitals and general practitioners, as well as his own experience, in treating arthritis. According to him the action of BV is better against RA than against OE.

Summarising all studies it can be concluded that BV can be used for the treatment of both types of arthritis, but RA seems to be more susceptible to BV.

Why BG is better than the hormone therapy against rheumatic pain?

Many researchers attribute the success of bee venom therapy to the activation of main hormone systems of the body: thyroid, pituitary gland, the hypothalamus and the adrenal gland. Hormone therapy, for example cortisone, ACTH hormone, are also applied against rheumatic pain. However, hormone therapy causes with time of use unfavorable side effects such as the reduction in the activity of this vital hormone glands, while the BV constantly activates the activity of hormonal systems.

BV against neurodegenerative diseases of the nervous system



Due to its different effects on the central and peripheral nervous system BV is also used for the treatment of different neurological conditions. There are reports on the use of different neurodegenerative diseases of the nervous system have been published, such as Multiple Sclerosis (MS), amyotrophic lateral sclerosis (ALS) Alzheimers and Parkinson, reviewed by Hwang et al. in 2015⁵²

Glutamate is the predominant excitatory neurotransmitter in the central nervous system (CNS). Changes in glutamate release and uptake due to alterations in the activity of glutamate transporters have been reported in many neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. To assess if BV can prevent glutamate-mediated neurotoxicity, we examined cell viability and signal transduction in glutamate-treated neuronal and microglial cells in the presence and absence of BV. We induced glutamatergic toxicity in neuronal cells and microglial cells and found that BV protected against cell death. Furthermore, BV significantly inhibited the cellular toxicity of glutamate, and pretreatment with BV altered MAP kinase activation (e.g., JNK, ERK, and p38) following exposure to glutamate. These findings suggest that treatment with BV may be helpful in reducing glutamatergic cell toxicity in neurodegenerative diseases⁸⁰

MS

The treatment of MS has raised attention in the recent years. The biggest study has been carried out by Ludyanski who report a very good or good improvement of 175 out of 210 cases (improvement rate was 83 %). Two studies, by Hauser et al. and by Castro et al. report improvement rates between 50 to 60 %^{15, 46}. A recent study by showed no significant effect of BV against MS, but the authors did not follow the protocol suggested by BV specialists¹²⁸. There is molecular basis for the action of BV for this action. Evidence of specific biologic effects of the BV component apamin in the brain, that might be linked to MS, has been shown^{35, 111, 123}. It was hypothesized that melittin and hyaluronidase are the anti-MS components⁶³

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system that leads to substantial disability through deficits of sensation and of motor, autonomic, and neuro-cognitive function. Many clinical and pathological features of experimental autoimmune encephalomyelitis (EAE) show close similarity to MS. Bee venom (BV) has been used in the practice of oriental medicine and evidence from the literature indicates that BV

plays an anti-inflammatory or anti-nociceptive role against inflammatory reactions associated with arthritis and other inflammatory diseases. The purpose of the present study was to determine whether BV could suppress immune cell differentiation and infiltration into spinal cord on EAE mice commonly used as a model for MS. BV treatment increased the population of CD4(+)CD25(+)Foxp3(+) T cells and inhibited CD4(+) T-cell proliferation in vitro. In vivo, BV treatment increased the population of CD4(+)CD25(+)Foxp3(+) T cells. Furthermore, BV administration reduced the severity of EAE while concurrently decreasing INF-gamma producing CD4(+) T cells, IL-17A producing CD4(+) T cells and inflammatory cytokine production including INF-gamma, IL-17A, TNF and IL-6. BV-treated animals exhibited less infiltration and preserved morphology compared to saline-treated animals. Interestingly, the therapeutic effects of BV on EAE disappeared when CD4(+)CD25(+)Foxp3(+) T cells were depleted by using anti-CD25 antibody. Our research suggests that BV could be a potential therapeutic agent for anti-inflammatory effects in an animal model of EAE⁷⁵

The experience of Krivopalov against MS ⁷¹

	Patient number	Improvement as a whole	Demyelination stop	Remyelination
Primary progressive	24	66 %	36 %	29 %
Secondary progressive	53	84 %	80 %	72 %
Relapsing	36	91 %	85 %	83 %

The above table summarises the experience on 113 patients in the Russian MS centre in Chelabinsk.

There is evidence specific effects of BV, especially of its component apamine on the CNS can be linked to MS^{36, 111, 123}. Also there are specific BV cellular anti-inflammatory action that might be linked to neurodegenerative processes^{27, 39, 91}

Parkinson

Bee venom reduces neuroinflammation in the MPTP-Induced Model of Parkinson's Disease in mice⁶⁵ and protects SH-SY5Y human neuroblastoma cells from 1-methyl-4-phenylpyridinium-induced apoptotic cell death²⁹ The BV-peptide Apamin has a neuro protective effect and can affect positively Parkinson. This was tested in animal models²⁸. In Parkinson mice models BV had a neuro-protective activity²¹. In another mice model experiment BV showed beneficial action on the pathological functioning of the cortico-basal ganglia circuits underlying motor PD symptoms with potential relevance to the symptomatic treatment of this disease⁸⁸

The Michael Fox Parkinson Foundation supports clinical research on the use of BG against Parkinson at the Pitie-Salpetriere hospital in Paris. On the basis of the clinical research an patient for the application using the injection of Apamin against Parkinson was submitted in January 2011 (Patent application number: 20110009330 from 01/13/2011). However in mice model experiments apamin reproduced these protective effects only partially, suggesting that other components of bee venom enhance the protective action of the peptide⁴

In Russia BV is successfully used in Parkinson's patients. After the Russian apitherapy school BV reduces the Parkinson symptoms. This effect is due to the positive biological effect of BV on the brain: the blood supply and the supply of dopamine in the brain is improved, it increases the brain blood vessels and reduces blood coagulation⁶².

A Korean study was conducted the effectiveness of both acupuncture and bee venom acupuncture as adjuvant therapies for idiopathic Parkinson's disease of 43 adults with idiopathic Parkinson's disease who had been on a stable dose of anti Parkinson medication for at least 1 month. They were randomly assigned to 1 of 3 groups: acupuncture, bee venom acupuncture, or control. All participants were assessed using the Unified Parkinson's Disease Rating Scale, the Parkinson's Disease Quality of Life Questionnaire, the Beck Depression Inventory, the Berg Balance Scale, and the time and number of steps required to walk 30 m. Treatment groups underwent stimulation of 10 acupuncture points using acupuncture or bee venom acupuncture twice a week for 8 weeks. The initial assessment was repeated at the completion of treatment. The control group did not receive any treatment. Participants in the bee venom acupuncture group showed significant improvement on the Unified Parkinson's Disease Rating Scale (total score, as well as parts II and III individually), the Berg Balance Scale, and the 30 m walking time. When compared to the control group, the bee venom acupuncture group experienced significantly greater improvement on the Unified Parkinson's Disease Rating Scale. In the acupuncture group, the Unified Parkinson's Disease Rating Scale (part III and total scores) and the Beck Depression Inventory showed significant improvement. The control group showed no significant changes in any outcome after 8 weeks. In this pilot study, both acupuncture and bee venom acupuncture showed promising results as adjuvant therapies for Parkinson's disease¹⁹

A neuroprotective effects of bee venom phospholipase 2 is postulated by suppression of neuroinflammatory responses in mouse model of Parkinson's disease²⁰ and ameliorates motor dysfunction and modulates microglia activation in Parkinson's disease alpha-synuclein transgenic mice¹³¹

Bee venom acupuncture had a neuroprotective effect in a mouse model of Parkinson¹³⁴

In another Korean study eleven patients (7 men and 4 women) with idiopathic PD who had been receiving a stable dose of anti-parkinsonian medication for at least 4 weeks. Participants received conventional treatment for 12 weeks. Subsequently, they received additional treatment with acupuncture and BVA twice weekly for 12 weeks while still maintaining conventional treatment. All participants were assessed at baseline, 12 weeks, and 24 weeks by using the Unified Parkinson's Disease Rating Scale (UPDRS), the Parkinson's Disease Quality of Life Questionnaire (PDQL), the speed and number of steps required to walk 20m, and the Beck Depression Inventory (BDI). Patients who underwent 12 weeks of twice-weekly combined treatment with acupuncture and BVA showed significant improvements in gait speed, PDQL score, activities of daily living (UPDRS part II), motor symptoms (UPDRS part III), and combined UPDRS part II+III scores compared with assessments after conventional treatment.²⁶

A prospective, randomized double-blind study was reported in 2016: 40 Parkinson disease patients at Hoehn & Yahr stages 1.5 to 3 who were either assigned to monthly bee venom injections or equivalent volumes of saline (treatment/placebo group: n = 20/20). The primary objective was to assess a potential symptomatic effect of s.c. bee venom injections (100 µg) compared to placebo 11 months after initiation of therapy on United Parkinson's Disease Rating Scale (UPDRS) III scores in the « off » condition pre-and post-injection at a 60 minute interval. Secondary objectives included the evolution of UPDRS III scores over the study period and [123I]-FP-CIT scans to evaluate disease progression. Finally, safety was assessed by monitoring specific IgE against bee venom and skin tests when necessary. After an 11 month period of monthly administration, bee venom did not significantly decrease UPDRS III scores in the « off » condition. Also, UPDRS III scores over the study course, and nuclear imaging, did not differ significantly between treatment groups. Four patients were excluded during the trial due to positive skin tests but no systemic allergic reaction was recorded. After an initial increase, specific IgE against bee venom decreased in all patients completing the trial. This study did not evidence any clear symptomatic or disease-modifying effects of monthly bee venom injections over an 11 month period compared to placebo using a standard bee venom allergy desensitization protocol in Parkinson disease patients. However, bee venom administration appeared safe in non-allergic subjects. It is suggested that higher administration frequency and possibly higher individual doses of bee venom may reveal its potency in treating Parkinson disease⁴⁵

Alzheimers

Several behavioral and electrophysiological studies indicate that small conductance calcium-activated potassium channels-blockade by apamin may enhance neuron excitability, synaptic plasticity, and long-term potentiation in the CA1 hippocampal region, and, for that reason, apamin has been proposed as a therapeutic agent in Alzheimer's disease treatment^{11, 54, 112}. Also BV phospholipase showed a neuroprotective effect in mice Alzheimers model⁷

A method for early diagnosis of Alzheimer with the help of apamin has been patented (US Patent documents 5580748; 5705401; 5778893 from 1999).

Individual reports on positive effects in dementia and Alzheimer have been reported by Ludyanski¹⁵ Specific brain effects of BV in Alzheimer patients have been elucidated⁵³ that might be linked to apamin action¹¹

Bee venom ameliorates cognitive dysfunction caused by neuroinflammation in an animal model of vascular dementia¹⁴

Bee venom phospholipase A2 has a neuroprotective effects of in the 3xTg AD mouse model of Alzheimer's disease¹³²

Other diseases of the nervous system

Against lower back pain

This topic was reviewed in 2015 by Lucache et al.⁸⁶. BV acupuncture was successfully used against chronic back pain and tested in two clinical trials^{117, 118}

Against post stroke shoulder pain

Lim and Lee reviewed in 2015 the clinical trials which tested the effect of application BVA in post stroke shoulder pain and concluded that it had positive effects⁸²

Neuroprotective action

Hypoxic-ischemic brain injuries influence the mechanisms of signal transduction, including mitogen-activated protein kinase (MAPK) that regulates gene expression through transcription factor activity. Several attempts have been made to use bee venom (BV) to treat neurological diseases. However, limited data are available for brain injuries such as neonatal hypoxic-ischemic encephalopathy (HIE) and neurodegenerative disorders. The purpose of this study was to investigate the neuroprotective effects of BV by determining the expression of activated MAPK pathways. The activation and cell viability in hypoxia (1% O₂, 5% CO₂, 94% N₂) in low glucose-treated (H+low G) neuronal cells and astrocytes in the presence and absence of BV was examined. After they were subjected to hypoxic conditions and treated with low glucose, the cells were maintained for 0, 6, 15, and 24 h under normoxic conditions. Extracellular-signal-regulated kinases 1/2 (ERK1/2), p38 MAPK, and stress-activated protein kinases (SAPK)/Jun amino-terminal kinases (JNK) were activated in H+low G conditions. Particularly, phosphorylation of ERK1/2 was maximized 6 h after exposure to H+low G condition. BV specifically inhibited the phosphorylation of ERK1/2. However, BV had no effect on p38 MAPK or SAPK/JNK. In addition, BV improved neuronal cell and astrocytes viability following exposure to H+low G. ERK inactivation is known to mediate protective effects in hypoxic brain injury. Taken together, these results suggest that treatment with BV may be helpful in reducing hypoxic injury in neonatal HIE through the ERK signaling pathway⁷².

Immunological diseases

The action of BV in immunological diseases has been reviewed by Hwang in 2015. BV therapy is a kind of allergen-specific immunotherapy. the immunological mechanisms of BV immunotherapy include a shift toward Th1 cytokines, an increase in the number of peripheral Tregs, and an upregulation of different markers expressed on CD4+ T cells. Also, phospholipase A2 and melittin have been linked in immunotherapy by their specific action⁵²

BV against the Lyme disease

BV, especially melittin inhibits the growth of Lyme disease spirochete, *Borrelia burgdorferi*^{84, 85}. Dr. Klinghardt on his homepage www.klinghardtacademy.com/Protocols/Neural-Therapy-with-Bee-Venom.html gives an exact protocol on the successful use of BV in combination with neural therapy.

Against HIV

Although melittin destroys the infectivity of HIV particles, the utility of this toxin is limited by its nonspecific cytotoxic effects: melittin kills cells by disrupting membrane structure and function. If administered directly to humans, melittin would kill any cell it encounters, causing widespread tissue damage. Therefore, researchers developed a method to deliver melittin by nano-particles so that it comes into contact with HIV particles, but not human cells⁵⁰

BV in cancer treatments

Strengthening the immune system by BV

It is known that BV has an immunostimulating effect. The weakened immune system of cancer patients was activated by BV¹⁰⁹.

It has been proposed that by increasing the immune response BV can help the body to fight the pandemic swine influenza A (H1N1)¹²⁰ (PSI) Russian apitherapists claim that by 5-6 BV prophylactic treatments the risk for getting PSI is significantly decreased (www.apiterapia.ru)

Against cancer

BV acts against different types of cancer in cell and animal experiments (see table 1).

A 2012 review by Orsolich with 183 references shows that BV and its components is a promising agent against cancer, however in most cases it has been tested in cells and animals tissue, thus clinical studies are needed The antitumor action seems to be due to the synergetic effect of melittin and phospholipase A2¹⁰³ A 2016 review by Liu et al. with 113 references gives a recent update of the state of the art of the use of BV and melittin in cancer treatment⁸³

It seems that melittin, a powerful anticancer peptide might be the better choice than whole BV. BV acupuncture and melittin were used to control neuropathy caused by cancer chemotherapy.^{104, 106}

However BV does not seem to have a cancer preventing effect as there was no difference between the cancer incidence of normal humans and beekeepers⁹⁰

Repetitive acupoint stimulation with BV gradually and significantly reduces oxaliplatin-induced mechanical allodynia and restores the loss of IENFs in neuropathic mice via an alpha-2 adrenoceptor mechanism. Collectively this study suggests that repetitive acupoint treatment with DBV can be a potential strategy for the management of chemotherapy induced neuropathy¹³³

Against traumatic injuries

Among 19 selected studies, all studies showed that BV therapy has significant effect on traumatic injury. This systematic review found encouraging but limited evidence of BV therapy for traumatic injury. Clinical trials which compare the effectiveness of Bee Venom therapy with other pharmacopuncture therapies to clarify the effectiveness of BV therapy from other pharmacopuncture therapies are recommended⁷⁷

Skin and eye diseases

Bee venom use against skin diseases has a long tradition and has been used since the beginning of the 20th century. Following skin diseases have been successfully treated eczemas like dermatitis, psoriasis, furunculosis (recurring boil), for the healing of cicatrices and against baldness. For skin application BV is applied in the form of creams and ointments and also in electrophoresis.

Six weeks of treatment with PBVTM serum was found to be effective in the treatment of mild-to-moderate acne vulgaris, with no incidence of serious side effects or irritation⁴¹

Interestingly enough BV has been used also in ophthalmology. Especially, it has been used for the treatment of acute and chronic rheumatic iritis and neuritis of the eye nerve. Aqueous BV solutions are used as drops and injections.

Bee venom in homeopathy

Bee and bee venom have been used as homeopathy remedies since Hahnemann (ca. 1800). In 1858 C.W.Wolf a prominent homeopathic physician of Berlin edited his book *Apis Mellifica or the poison of the honey bee considered as a therapeutic agent*. The principle of Apis application was reviewed in 1880 by Goullon³⁴ In homeopathical preparations whole bees are generally used in different potencies, both lower D and higher C potencies. Today whole bees are used for the homeopathic preparations

The Gale encyclopedia of alternative medicine, [online](#) see²⁴ states:

"Homeopathic medicine operates on the principle that "like heals like." This means that a disease can be cured by treating it with products that produce the same symptoms as the disease. These products follow another homeopathic law, the Law of Infinitesimals. In opposition to traditional medicine, the Law of Infinitesimals states that the lower a dose of curative, the more effective it is. To make a homeopathic remedy, the curative is diluted many, many times until only a tiny amount remains in a huge amount of the diluting liquid.

In about 1900, both bee venom and tincture from the entire insect were proved as a remedy by the Central New York State Homeopathic Society. In homeopathic medicine, Apis is used as a remedy for many symptoms similar to those of bee stings. These include:

- * inflammation with a burning sensation, * stinging pain * itchy skin*
- * swollen and sensitive skin * red, flushed, hot face * hive-like welts on the skin*

Homeopathic practitioners use Apis when stinging or burning inflammations appear in all parts of the body, not just on the skin. A homeopath could use Apis for sore throats, mumps, urinary tract infections, and other conditions where there is a stinging or burning sensation.

Symptoms treated by Apis usually appear quite rapidly. There is usually some swelling or edema along with the stinging sensation. Many people who need Apis complain of swollen eyelids, as if they had an eye infection. In keeping with the symptom of oedema, often little urine is produced although there may be a strong urge to urinate. Despite this, the patient has little thirst or desire to drink.

Often the patient who will be given Apis appears flushed or has a rough rash. The rash may appear, then disappear. The skin will be sensitive to the touch and alternatively hot and dry, then sweaty. Patients may also feel nauseated, suffer from heartburn, or have tightness throughout their chest or abdomen that feels like they will burst if they cough or strain.

Certain mental and emotional symptoms also appear in the patient that needs Apis. Sadness, weeping, and depression can occur. Apis is often used after a person experiences a strong emotional reaction such as jealousy, fear, rage, or anger.

In homeopathic medicine, the fact that certain symptoms get better or worse under different conditions is used as a diagnostic tool to indicate what remedy will be most effective. Symptoms that benefit from treatment with Apis get worse by applying warmth or drinking warm liquids. They also get worse from touch or pressure, or when the person is in a closed, heated room. The symptoms are often worse on the right side, after sleeping, and in the late afternoon. Symptoms improve with the application of cold and exposure to open air.

The Apis personality

is said to be fidgety, restless, and unpredictable. People with the Apis personality may have wildly inappropriate reactions to emotional situations. They want company, but reject affection, and sometimes insist that they don't need medical attention when they are clearly unwell. People who need Apis often have bouts of unprovoked jealousy and unprovoked tears. They may fear ill health and death greatly.

Precautions

No particular precautions have been noted for using Apis. However, people who are allergic or sensitive to bee venom should be cautious. They may react adversely to certain potencies of homeopathic Apis.

Side effects

When taken in the recommended dilute form, no side effects from Apis have been reported. However, concentrated quantities of the bee venom can cause allergic reactions in susceptible people.”

Preparations

There are two homeopathic dilution scales, the decimal (x) scale with a dilution of 1:10 and the centesimal (c) scale with a dilution factor of 1:100. Once the mixture is diluted, shaken, strained, then rediluted many times to reach the desired degree of potency, the final mixture is added to lactose (a type of sugar) tablets or pellets. These are then stored away from light. Homeopathic Apis venom is available commercially in tablets in many different strengths. Dosage depends on the symptoms being treated. Homeopathic tincture of whole honeybees is also available in a variety of strengths.”

Apis preparations can also be used for many indications, according to a recent homeopathic report by Schraner, 2007¹¹⁵, downloadable at www.emindex.ch/gregor.schraner against:

- Inflammation diseases of eyes, ears, respiration organs,
- Diseases of digestions organs, bladder, kidney
- Skin diseases, allergies, acne, abscesses
- Scarlet and German measles, diphtheria,
- Glandular and genital diseases
- Heart and blood circulation diseases
- Psychiatric diseases

The Russian experience

Treatments of many other diseases reviewed in different Russian monographs^{70, 71, 87, 114}, see tables 3 and 5. The Russian doctor Ludyanski has summarised his experience of the application of BV in a big Russian hospital¹⁸

Apitherapy of different diseases with BV in a Russian hospital after Ludyanski

Disease	Very good success	Good success	No change
Polyarthritis	77	18	15
Osteochochrosis (orthopedic disease)	1542	352	116
Bronchial asthma	38	17	10
Hypertension	18	9	18
Multiple sclerosis	103	72	35
Post stroke paralysis	196	10	31
Polyneuritis	22	9	6
Ganglion nerve inflammation	11	4	1

Cerebellar ataxy (muscular disfunction)	12	7	2
Syringomyelia (pain of extremities, headache)	140	31	11
Inflammation of facial nerve	128	6	1
Myopathy (neuromuscular disease)	54	8	16
Trigeminal neuralgia	16	7	2
Post-traumatic inflammation of the plexus nerve	206	46	21
Arachinoid inflammation (a CNS membrane)	275	20	20

BEE VENOM AND COSMETICS



Bee venom has been claimed to be the new Botox. This claim has a new prominent support in the name of Camilla Parker-Bowles, Duchess of Cornwall and wife of Prince Charles (see below)

Honey bee venom is used cosmetically to 'fool' the skin into thinking it has been lightly stung with the toxin melittin. This causes the body to direct blood towards the area and stimulates the production of the naturally-occurring chemicals collagen and elastin. Collagen strengthens body tissue while elastin is the protein that helps the skin to remain taut and bounce back into shape after being pressed or pinched. The venom also has the effect of relaxing the muscles, it is claimed

The antiaging Heaven BV mask should be used as follows:

Apply BV mask to cleansed skin, leave for 20 minutes then wash off, thereafter daily use massage a small amount onto the skin morning or evening or apply a thin layer under make-up for a flawless finish.

A Skin sensitization study of BV was carried in guinea pigs and rats which showed that that BV was well tolerated and exhibited no dermal irritation potential in guinea pigs and rats. The findings may provide a developmental basis of BV for a cosmetic ingredient or external application for topical uses⁴²

The positive effect of BV against aging related human face wrinkles has been scientifically proven⁴⁴

APPLICATIONS AND TREATMENT FORMS

There is a big experience on the use of BV in medicine in Russia^{62, 70, 87}. Ludyanski reviews in his monograph the use of BV, in practically all medical disciplines⁸⁷. However, this work is in Russian and not easily accessible. Khismatullina has summarised the knowledge of Russian apitherapy in her book on Apitherapy⁶².

The therapeutical dose of BV is much lower than the toxic one. Apitherapy with BV should be applied by medical doctors, because of the dangers connected with this treatment (see allergy reactions).

For apitherapy purposes different applications forms have been used:

- Puncture with whole bees: in non specific or in specific points and zones
- The Iorish technique: stings are applied to the outer surface of shoulders and thighs. Number of bees is gradually increased to 10 bees to the 10th day, then take a break of 3-4 days. After the break the number of bees is decreased from 10 to 1 during 10 days.
- The Kuzmina technique: number of bees is gradually increased to 10 bees to the 10th day, then take a break of 3-4 days. Then the number of bees is increased by 3 in every session (3, 6, 9, 12, 15..... 30)
- Micropuncture with the BV stinger
- Injections with pure, sterile BV
- Apipuncture (apitoxinreflexotherapy)
- BV ointments, creams, pills, drops
- Apis homeopathic preparations
- Electrophoresis, phonophoresis

Therapeutic index

As other highly effective drugs, bee venom, too, has various side effects. Often the therapeutic and the toxic effects lie closely together. Individual BV components show toxic effects when their concentration is 20-50 times greater than the therapeutic dose, while whole bee venom is toxic when its therapeutic dose is exceeded by 200-500

times¹¹⁹. In conclusion, for general therapeutical purposes BV is safer to use, while for specific medical applications BV components seem to be preferable

Application of BV components

Two of the principal and biologically active BV components melittin and apamin are commercially available and can be used for therapy instead of the whole BV. Melittin can be combined to a low molecular polysaccharide fucoidan for a reduced toxicity⁸⁹. The clinical application of melittin and apamin has been reviewed by Moreno and Giralt in 2015⁹²

Phospholipase A2, the major allergenic component of BV, can be separated from whole BV by ultrafiltration, the resulting BV has a much smaller sensitizing potential⁴⁹

Bee Venom Acupuncture (BVA) or Apipuncture is described in detail by Ludyanski⁸⁷ and in principle also by Yoshimoto¹³⁵, is reviewed by Lee⁷⁹. In China a book by Chen Wei “Chinese Bee Acupuncture” has been published¹⁷ Both stings by bees and injection into acupuncture points are used.

The clinical application of BVA in South Korea was reviewed by Han et al. in 2015 with 235 reviewed clinical studies³⁸

Dose

The **applied doses** for adults are generally between 0.1-3 mg BV per treatments, the dose depending on the disease, higher doses (until 2-2.5 per treatment) being used in arthritis treatments⁸⁷. In one sting the maximum of about 50 to 100 µg per are applied, in micropuncture much less BV is applied, depending on the stinging time about 1 to 10 µg can be applied. The lethal dose is about 2.8 mg/kg or 19 stings per kg, for a man of 75 kg meaning about 1400 stings.



Application of whole bee stings



Micro-stings



BV powder



BV pellet



BV cream



BV eye drops



BV homeopathic solution



Apis D6



Apis C30



Honey and BV

ADVERSE REACTIONS, COUNTER-INDICATIONS AND ALLERGY

BV stings and injections cause different adverse reaction.

The first and prominent effect is the induction of **pain**, produced mainly by melittin¹⁶

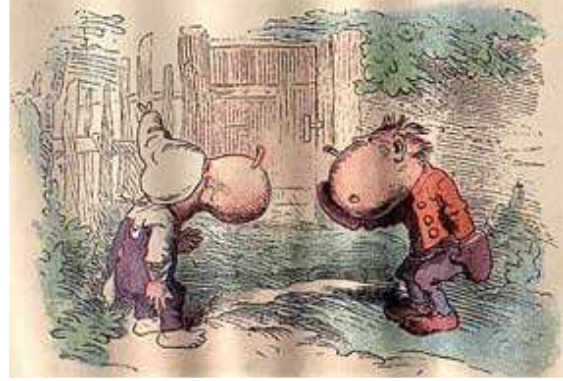
The **safety** of bee venom as a therapeutic compound has been extensively studied, and reviewed by Park et al in 2015. This resulted in the identification of potential adverse events, which range from trivial skin reactions that usually resolve over several days to life-threatening severe immunological responses such as anaphylaxis. In this systematic review, a summary of the types and prevalence of adverse events associated with bee venom therapy has been made¹⁰⁷

Counter indications

The main counter indication to BV therapy is bee venom allergy. Apitherapy should be used only after a bv allergy test. Bee venom therapy is counter-indicated under following conditions:

- During acute and chronic infections
- After vaccinations
- Chronic tuberculosis and hepatitis
- Acute cancer
- Children under 5 years old
- Pregnancy, breast feeding
- Type 1 pancreatic diabetes
- Renal insufficiency, hepatic failure, impaired cardiac functions and respiratory problems

REACTIONS TO BEE STINGS AND BEE VENOM ALLERGY



The little honey thieves, by Wilhelm Bush, 1865

The most outstanding biological effect of bee venom is the painful inflammation, caused by the bee sting. What should be done after a bee sting? Normally, „only“ strong swelling is caused at the point of stinging. A threatening toxic reaction can be caused after more than 50 stings (for children) and more than 100-500 for grown-ups. In this case the patients should be hospitalised.

A bee sting in a normal person

(Fotos and comment from Wikipedia, the free encyclopaedia, October 2009)



The stinger is torn off and left in the skin



2 minutes later



6 minutes later, after the sting has been removed



27 minutes later

Dangerous stings at the area of the eyes and mouth.

Stings in the area of the eyes, the temple are always dangerous because of the strong pain and swelling and require an immediate medical help. As an immediate measure the eye should be rinsed with cold water until the pain eases.

Stings on the tongue or the pharynx are especially dangerous. Because of the rapid swelling of the mucous membrane there is an acute life threat by suffocation. Only the emergency medical doctor can help. Until he comes the patient should suck a piece of ice or should consume ice-cold drinks to prevent the spreading of the swelling.



A sting in the eye area

Stings in the area of the eyes, the temple are always dangerous because of the strong pain and swelling and require immediate medical help. As an immediate measure the eye should be rinsed with cold water until the pain eases.

Photo courtesy U. Mueller.

Help after a bee sting

Removal of sting: When a human is stung by a bee, the sting with the sting apparatus remains stuck in the skin. *First the sting should be removed as soon as possible*, for that purpose it should be pushed away from the side with the finger nail. Be aware that pressing the sting with both fingers will cause emptying of the bee venom into the tissue.

Cooling: Afterwards the stung area should be cooled by means of a cold compress with acid water (1 part of vinegar and 2 parts of water), ice cubes, cold spray or alcohol. Also, application of onion strips or propolis tincture can help. Apply an anti-allergic gel if available.

Doctor's visit: If the swelling and pains increase and/or if a red strip under the skin persists one day after the sting, a doctor should be called. Normally, these troubles diminish 1-3 days after the sting.

after Mueller⁹⁷⁻⁹⁹

Emergency aid for persons allergic to bee venom

- **Take prescribed tablets** immediately after bee sting, by
- **Prepare adrenalin self-injectible ampoule** (e.g. EpiPen®), if a general reaction like redness, swelling, shivering, vomiting, nausea, shortage of breath, arises, and apply it immediately (intramuscularly or subcutaneously)
- **Call the emergency doctor** after the slightest symptoms of a general reaction, to avoid complications, which can, in the extreme case, be lethal.
- **Lay the shocked patient**, warmly covered, on a flat surface. If a heart- or breath stop occurs, mouth-to-mouth breathing and a heart massage should be performed by trained persons until the arrival of the emergency doctors, who will perform all other necessary measures.

after Mueller⁹⁷⁻⁹⁹

Bee stings and bee venom allergy

This topic has been reviewed by Mueller in 2010. Bee stings are especially dangerous for allergic people. According to different studies 1 to 5 % of the people world wide are allergic to bees or other insects like wasps and hornets⁹⁵, but a 2012 review on the subject states that the numbers are higher, up to 25 % of the population, while anaphylaxis is about 3.5 %¹⁰⁸

There are different grades of allergic reactions and in the worst case a bee sting can lead to death. In Switzerland, one person dies every year after a sting of a bee or a wasp¹¹³. Beekeepers are specially exposed to bee stings. The

development of a bee venom allergy is less probable if they are stung more often. Beekeepers with more than 200 annual stings will never develop a BV allergy⁹⁷. However, beekeepers and their family members are at an increased risk of severe sting anaphylaxis and therefore need especially careful instruction with regard to avoidance of re-exposure, emergency treatment and specific immunotherapy with bee venom⁹⁶.

There are two types of allergic reactions: a heavy local reaction and a general allergic reaction.

Heavy local reaction:

After a sting the redness does not remain local, but expands over the extremities. The swellings can be very painful and can persist for a longer period of time.

General reaction

The first symptoms arise a few minutes after the sting. They can be accompanied by shivering, vomiting, nausea, shortage of breath. The main symptoms are redness, swelling and itching. They can be accompanied by strong swelling of the face. In the worst case a life endangering collapse of blood circulation can occur – the anaphylactic shock.

All persons, allergic to BV should possess first help medication kit, composed with the help of the doctor (see box). If the reaction to a bee sting does not fade away rapidly, an emergency doctor should be called. As the symptoms of a heavy allergic reaction can arise within minutes, a medication with rapid effect should be applied immediately (see box).

Desensitisation

Persons with bee venom allergy can be desensitised. The success of the desensitisation against bee venom is about 80 %, while that against wasp venom allergy is approx. 95 %¹¹⁰.

It was shown that beekeepers can be successfully desensitized and can continue their activity after desensitization, a complete absence of symptoms after re-exposure to bee stings can be achieved¹⁰⁰

Three to five years are necessary for a secure and durable desensitisation. A desensitisation is absolutely recommended. Compared to other bee venom allergic persons beekeepers had a better desensitisation success. Older allergic persons are especially endangered towards bee stings and should absolutely be desensitised³¹. Specially prepared BV is used for desensitisation¹²⁵

Further Reading:

BV properties and apitherapy ^{6, 9, 10, 10, 30, 70, 79, 87, 97, 101, 116, 122, 127}

Desensitisation ^{95, 97-99}

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